Assessing uncertainties in the relationship between inhaled particle concentrations, internal deposition, and health effects.

Chapter for Aerosol Handbook.

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Introduction

The question that ultimately motivates most aerosol inhalation research is: for a given inhaled atmosphere, what health effects will result in a specified population? To attempt to address this question, quantitative research on inhaled aerosols has been performed for at least fifty years (Landahl et al, 1951). The physical factors that determine particle deposition have been determined, lung morphology has been quantified (particularly for adults), models of total particle deposition have been created and validated, and a large variety of inhalation experiments have been performed. However many basic questions remain, some of which are identified by the U.S. Committee on Research Priorities for Airborne Particulate Matter (NRC 1998a) as high-priority research areas. Among these are: What are the quantitative relationships between outdoor concentrations measured at stationary monitoring stations, and actual personal exposures? What are the exposures to biologically important constituents of particulate matter that cause responses in potentially susceptible subpopulations and the general population? What is the role of physicochemical characteristics of particulate matter in causing adverse health effects? As these questions show, in spite of significant progress in all areas of aerosol research, many of the most important practical questions remain unanswered or inadequately answered.

In this chapter, we discuss the sources and magnitudes of error that hinder the ability to answer basic questions concerning the health effects of inhaled aerosols. We first consider the phenomena that affect the epidemiological studies, starting with studies of residential radon and moving on to fine particle air pollution. Next we discuss the major uncertainties in physical and physiological modeling of the causal chain that leads from inhaled aerosol concentration, to deposition in the airway, to time-dependent dose (that is, the concentration of particles at a given point in the lungs as function of time), to physiological effects, and finally to health effect.

Figure 1 illustrates, in greatly simplified form, the various factors that affect the relationship between exposure and health effects, as well as the measurements of those factors. For instance, the aerosol size and type distribution in the breathing zone is a factor that directly influences deposition in the respiratory tract, but parameters can be directly observed only at a sampling location, which may or may not sample the breathing zone. The network of rectangular boxes in the central column of the figure shows the causal chain that controls the relationship between aerosol exposure, dose, and ultimately health effects. To first order, all connections move down the chain: size distribution, inhalation details, and respiratory tract morphology control deposition, which, combined with clearance, affects dose, and so on. Connections can run the other direction too, as shown by the non-bold arrows on the figure: physiological effects can change the clearance rate and the inhalation rate. These effects can be quite important for large exposures to irritating compounds.

<INSERT FIGURE 1 ABOUT HERE>

For a given inhaled atmosphere, what health effects will result in a specified population? The simplest attempts (at least conceptually) to address this question are epidemiological studies. Epidemiological studies directly investigate the statistical relationship between aerosol measurements and health outcomes is investigated directly, without attempting to model the causal chain that connects these parameters. Examples include studies on the relationship between radon (and its decay products) and lung cancer, both in miners and in the general population, and also studies on the relationship between outdoor aerosols and morbidity or mortality in the general population, as determined from hospital records or death certificates respectively.

Should we worry about dose or about exposure?

We will not attempt a technical definition of "dose," but generally speaking we mean the biologically significant quantity of particles delivered to a given part of the respiratory tract, so that dose may be a function of location. Determination of dose is very difficult, because dose is almost impossible to measure directly (except in the case of some radioactive particles). Most studies, including essentially all epidemiological studies, use a surrogate measure, "exposure," which is the time-integrated concentration of a pollutant in the subject's breathing air. Individuals with the same exposure might experience a very different dose: a large person performing exercise and breathing hard through the mouth will receive a different dose from that received by a small resting person breathing shallowly through the nose, even if they are breathing the same air.

Many questions in applied aerosol inhalation concern the relationship between *exposure* and health effects: what regulatory limits (if any) should be placed on pollutant emissions, what airborne pollutant concentration limits should be set by the Clean Air Act, at what indoor radon concentration should remediation be performed, and so on. From the point of view of a regulatory agency or an industrial hygienist, the knowledge that a particular quantity of a given pollutant, if deposited in the lower respiratory tract, will produce a particular health outcome, is almost immaterial. What they really want to know is, what is an acceptable concentration of the pollutant in the air.

Since the relationship between exposure and health effect is often the question of interest, it is tempting to think that the difficult issue of true dosimetry (as opposed to exposure assessment) can be avoided altogether. Why not simply perform all experiments, case-control analyses, etc., in terms of exposure? The answer is that, because biological effects are caused by dose and not exposure, knowledge of the dose-response relationship can be used to answer questions that knowledge of the exposure-response relationship cannot resolve.

One situation in which an understanding of dose rather than merely exposure is required is the extrapolation of experimental results to different populations or environmental conditions. For example, data on miners exposed to high levels of radioactive aerosols produced by radon decay demonstrates quite convincingly that very high levels of exposure cause lung cancer, and that risk increases with exposure (see Lubin et al. 1995 for an overview, and Kusiak et al,1993, Howe et al. 1986, Howe et al. 1987, Tomasek et al. 1994, and many others for original reports). What relevance, if any, do these results

have for residential concentrations, which are typically lower by a factor of 100 or more? Working miners breathe much harder than most people, are simultaneously exposed to large concentrations of other (non-radioactive aerosols), and experience a different relationship between radon concentrations (the quantity that is measured) and radon decay product concentrations (which actually provide the radioactive dose to the lung). Consequently, extrapolation to the general population is quite challenging. Similar issues arise in exposures to industrial compounds, for which extrapolation is usually required in order to apply observational results from exposed workers to the general population.

Another situation that requires an understanding of dose is airborne delivery of drugs such as asthma medicine: What particle size will be most efficient, how will the answer vary with health status (e.g. ability to take a deep breath), and so forth, are questions that require an understanding of the full relationship between exposure, dose, and health effect, not just exposure and health effect.

Generally speaking, observational data on the exposure-response relationship for a pollutant can be sufficient to roughly characterize the relationship in the regime in which health effects are very large, but such data cannot definitively address the relationship for much smaller exposures; for that, an understanding of some or all of the causal chain is required.

Epidemiological Studies

Epidemiological approaches to determining the health effects from airborne particles attempt to avoid the "how and why"---the network of physical and physiological connections shown in Figure 1---and instead directly investigate the matter of ultimate interest: what are the adverse outcomes (if any) from human exposure to aerosols?

Epidemiological studies of the health effects of aerosols fall into four categories:

1. Case-control studies that relate observed health outcomes to past particle exposures of cases (people with a particular health problem) and controls (people without the problem). Do sick people have higher exposure than healthy people? Or, equivalently as it turns out, are more highly exposed people more likely to become sick?
2. "Ecological" studies that compare long-term aerosol data, and long-term data on health outcomes, across cities or regions that have different airborne particulate concentration. The essential question here is: Where airborne particle concentrations are higher, are people sicker?
3. Time-series studies that compare time-resolved aerosol data to time-resolved data on health outcomes, for a particular location or region. *When* airborne particle concentrations are higher, are people sicker?
4. Cohort studies that select a group of subjects and track them (ideally until death), and look for a difference in health effects as a function of exposure. Does the chance that someone will get sick depend on the particle concentrations to which they're exposed?

Unfortunately, all of these approaches have serious practical shortcomings. Case-control studies usually require retrospective assessment of exposures, often reaching far into the

past, a task always subject to large errors. Ecological studies face an inherent problem known as the "ecological fallacy," which will be discussed below, and which renders such studies suitable for hypothesis testing and perhaps consistency testing rather than quantitative risk assessment. Time-series studies are probably the best choice for practical quantitative risk assessment of acute aerosol exposures, but as discussed below they can be subject to confounding variables, they often have low statistical power, and they cannot provide risk estimates for chronic exposure. Cohort studies are subject to confounding because highly exposed cohorts often differ from less-exposed cohorts in ways other than exposure, not all of which can be controlled. Also, cohort studies are limited in practice because they require a decades-long commitment to track the subjects after exposure. For this reason cohort studies are normally possible only when exposure monitoring is performed as a matter of course (as was the case for some miner studies of radon), so that monitoring data can later be opportunistically used to perform a retrospective study long after the exposures occurred.

Radon epidemiology

Background:

Inhalation of radioactive aerosols has been an area of intensive research. In the past twenty years or so, much of this research has been motivated by the study of indoor radon and its decay products. Radon is a naturally occurring radioactive gas whose decay products, which are themselves radioactive, provide most of the radiation to which people are exposed in their life, and there is considerable interest in quantifying the exposures and the dose-response relationship. The vast majority of research in this area uses radon measurements in an attempt to quantify risk, rather than measurements of radon decay products themselves, even though it is the decay products rather than radon itself that are responsible for the radiation dose. The ratio of total airborne activity concentration to the radon activity concentration is known as the "equilibrium factor," and varies with time and from home to home (e.g. Huet et al. 2001, El-Hussein et al. 1998), increasing along with the particle concentration in indoor air. However, as discussed by James (1988) the dose delivered to the lung is controlled by the radon decay products that are "unattached" (not stuck to coarse aerosol particles), which varies inversely with equilibrium factor so that the dose for a given radon concentration is roughly independent of room conditions, for conditions typically found in homes.

Convincing evidence of radon-related lung cancer was found in miners, who were found to be at substantial excess risk of lung cancer, and whose risk was found to increase with increasing cumulative exposure to radon and thus, presumably, its decay products; however, the relationship between airborne concentrations of radon to its inhalable decay products is much more complicated in mines than in homes for reasons involving the high airborne particle concentrations in mines. Also, estimates of radon concentrations to which miners were exposed are very uncertain. Therefore, although high levels of radon were convincingly shown to be associated with increased lung cancer risk, the relationship between cumulative exposure and increased risk was (and remains) uncertain by at least a factor of three. See Steinhausler (1988) for a discussion of many of these issues, with data.

In the past twenty-five years concern has shifted from miners to the general population. Indoor radon concentrations are much lower than those in mines, but are not necessarily negligible. Extrapolation of risk from miner data is problematic, because miners were subject to very high radon exposure and were simultaneously exposed to other materials (such as dust, engine exhaust, etc.), in addition to having more, and longer, periods of deep breathing. Adjusting for these factors as well as possible, and (importantly) assuming a linear dose-response for inhaled radon decay products, led to predictions, albeit highly uncertain ones, for risk per unit dose for both smokers and non-smokers in residences.

Indoor radon concentrations are highly variable. In the U.S., annual-average living-area radon concentrations are approximately lognormally distributed (Marcinowski et al. 1994) with a geometric mean of about 26 Bq/m^3 and a geometric standard deviation (GSD) of about 3.1. Even small areas are quite variable; for example, living-area average radon concentrations within most U.S. counties are approximately lognormally distributed with a geometric standard deviation (GSD) near 2.2.

When applied to the statistical distribution of radon and smoking in the U.S., model predictions based on extrapolated miner data suggested that between 10,000 and 20,000 people die per year due to inhaled radon decay products; most of the predicted deaths are among smokers, and these figures are derived from an unrealistic comparison to the number of people expected to die of lung cancer if no one were exposed to any radon (or radon decay products) whatsoever.

Epidemiological studies have attempted to determine the dose-response relationship (or, more correctly, the exposure-response relationship) for the range of radon exposures that occurs in residences. Radon research has included three of the four types of epidemiological studies mentioned above: (1) case-control studies, in which the radon exposures of individuals with lung cancer are compared with those who do not have lung cancer, (2) “ecological” studies that compare average lung cancer risk with average radon exposure, typically by county, and (3) cohort studies that attempt to follow until death cohorts of miners which were exposed to different radon concentrations, and look for a difference in lung cancer rates attributable to exposure. The challenges of quantifying miner exposures (and, even more difficult, doses) are very interesting, but we choose to focus here on residential exposures and will not discuss the miner studies.

Case-control studies of residential radon

Figure 2 shows the estimated odds ratios, with 95% confidence intervals, for different exposure bins, found by five case-control studies involving residential exposure to radon. Although these are arguably the best studies in terms of estimating exposures and avoiding other sources of error, this does not constitute a comprehensive list of studies of this type; see Field (2001) and Lubin and Boice (1997), which summarize results of some more case-control studies. The statistical distribution of annual-average living-area mean radon concentrations in the U.S. is shown at the bottom of the figure (arbitrary vertical scale).

<INSERT FIGURE 2 ABOUT HERE>

Even the seemingly straightforward task of plotting results from different radon case-control studies on a common scale can be tricky: each study used different exposure bins, some used different methods of determining how exposures would be binned (e.g. using average exposure over the past 25 years, or over the time period from 5 to 25 years ago), each study calculated the odds ratio relative to the lowest exposure bin (rather than to a group of people who were exposed to no radon, since such a group does not exist) and the exposure range for the lowest bin is different for each study, and so forth. Figure 2 does not attempt to adjust for these issues. For each study, the overall odds ratio (not separate odds for smokers and nonsmokers) is plotted for each bin at the mean radon concentration for subjects within that bin.

A line labeled "Theory" and representing approximately the extrapolation from miner studies (NRC 1998b), which we will call the "standard model," is superimposed on the plot (actually the theory predicts relative risk, not odds ratio, a technical difference that should show a very slight downward curvature to the line, which we have not bothered to include). The plot shows the predicted odds ratio as a function of radon exposure for the U.S. proportion of smokers and nonsmokers; even if a linear response is assumed the slope of this line is uncertain by at least a factor of three. All of the studies are consistent with the prediction from the standard model, but are also consistent, or nearly consistent, with radon having no effect on lung cancer (an odds ratio of unity) over the range of radon exposures tested. The studies that do find a "statistically significant" ($p < 0.05$) increase in lung cancer for increased radon concentration do so only for the highest exposure bin or two, and only by a bare margin. This does not, of course, indicate that there is no effect at lower concentrations --- as the size of the error bars illustrates, each individual study has very low statistical power.

Lubin and Boice (1997) performed a meta-analysis of eight epidemiological studies, including several not shown on Figure 2, but failing to include recent studies from China (Wang et al., 2002) and Iowa (Field et al., 1999) which were not available at the time they wrote their paper. They concluded that the best-fitting linear dose-response model is remarkably close to the best-guess extrapolation from miner data (the "Model" line on Figure 2), but that the 95% confidence intervals barely exclude "no effect"; looking at categorical rather than continuous effects, the relative risk at 150 Bq/m^3 is estimated to be 1.14, but with a 95% confidence interval from 1.01—1.30, thus barely excluding unity. The more recent results from the studies in Iowa and China would narrow the error bars slightly without substantially changing the central estimates.

Sources of error in exposure estimates in case-control studies of residential radon
The following are some of the major sources of error for residential radon case-control studies.

1. Population mobility: people change residences, so monitoring in the current residence will not generally provide a good estimate of long-term exposure. Each study had some method for minimizing the influence of this fact, e.g. by studying

only subjects who had long lived in the same home for many years (Field et al., 2000), by monitoring in all past homes (Lagarde et al., 1997), or both (Wang et al., 2002). In all studies (other than Iowa), some homes could not be monitored and the missing data were imputed.

2. Long-term temporal variability in radon concentrations: current monitoring in a home does not accurately estimate the past radon concentration in the home. Concentrations are known to vary from year to year; Steck (1994) found about 25% year-to-year variation in a study of 100 homes in Minnesota. Two studies have attempted to avoid this problem: in addition to the conventional use of radon detectors to monitor individual homes, both the Iowa study (Field et al., 2000) and a Missouri study (Alavanja et al., 1999, not included in Figure 2) used conventional radon monitors but also used a novel exposure assessment technique based on accumulation of a long-lived radon decay product, Lead-210, in one or more glass objects belonging to a home's residents. These measurements are thought to reflect the long-term average radon concentration to which the object was exposed, which is assumed to be related to the owner's radon exposure. (In both studies the result was a slight increase in estimated risk).
3. Spatial variability of radon concentrations within the home: people spend time in different rooms on different floors of their house, so a house-average radon concentration will not accurately estimate personal exposure. The Iowa study (Field et al., 2000) attempted to avoid this problem by adjusting for the fraction of time subjects spent in each area of their home, at different periods of their lives. Most other studies neglect the effect of mobility within the home.
4. Interviewer bias or respondent bias in questions regarding smoking or other risk factors: cases may respond differently from controls. Questions related to lifetime cigarette smoking, or other perceived risk factors such as time spent in the basement, may be more likely to draw biased answers from cases than controls, or vice versa.
5. Uncontrolled or inadequately controlled confounding variables: the populations of cases and controls can differ in many ways, due to both biases in selection procedures and to random chance. Information on known or suspected confounding variables is collected and used to attempt to control for such variables, e.g. by adjusting for age, stratifying by smoking status, and so on, but may not completely remove the confounding effects.

Sources of exposure error such as items 1—4 can cause three problems. First is the potential for bias: if any of the errors systematically over- or under-estimates radon exposure for cases compared to controls, this will bias estimates of risk, a particular problem if the risk is small or the bias is large. Second is the problem of statistical power: the more noise, the less ability to distinguish a small signal, and the more cases and controls are necessary. Third, and the most tractable if the magnitudes of the error can be estimated, is that random errors in exposure will yield an exposure-risk curve that is too flat: high-estimated-exposure categories will tend to contain subjects whose exposure is overestimated, and low-estimated-exposure categories will tend to contain subjects whose exposure is underestimated. If the magnitudes of the errors are known, however, the effect can be removed statistically (e.g. Field et al., 2997). Conceptually, the points to the right in Figure 2 need to be shifted slightly to the left, and the points at

the left need to be shifted slightly to the right; this will yield a higher estimate of the slope, but will not improve the statistical power.

Sources of exposure error as discussed above can shift invdividual or group exposure estimates up or down, corresponding to moving to the left or right on Figure 2, usually tending to weaken the relationship between exposure and health effects. Confounding variables, on the other hand (item 5) can shift estimates up or down, and can thus totally change the exposure-response effect. The possibility of such confounding is ignored in the uncertainties quoted for the different studies, since after all the whole point of a case-control design is to try to eliminate this effect, but in practice this is always a concern and the true uncertainty for each bin should be expanded somewhat.

Lubin et al. (1995) used a simulation method to determine the statistical power of case-control studies in the presence of population mobility and exposure estimate error. They concluded that for normal mobility and typical U.S. radon exposures a case-control study would require somewhere in the range of 5,000 to 13,000 cases (and about twice as many controls) in order to convincingly demonstrate increased radon risk at an exposure of 150 Bq/m^3, even if the standard model is correct. That number of cases would be vastly more than the number for any single case-control study that has been performed so far. Indeed even the total number of cases in all of the case-control studies performed so far barely reaches the low end of this range, including 4,236 cases in the eight studies examined by Lubin and Boice (1997), 413 in the Iowa study (Field et al., 2000), and 886 in the China study (Wang et al., 2002). Note, however, that the Iowa and China studies specifically selected low-mobility, highly exposed populations, thus decreasing exposure errors and increasing the expected risk, so that fewer cases would be needed to demonstrate an effect.

Overall, the case-control studies seem to indicate a slightly elevated risk of lung cancer for long-term exposure averaging over 150 Bq/m^3. The case-control results are consistent with the standard model, but they do not have sufficient statistical power to rule out a threshold below which there is no effect (or even a small protective effect), and are certainly consistent with risks much smaller than predicted by the standard model. In short, although case-control studies of radon can be informative for very high exposures and high risks, it seems unlikely that they will ever be able to provide reliable risk estimates below several hundred Bq/m^3.

Ecological studies of residential radon

A series of papers by Cohen (e.g. Cohen and Colditz 1994, Cohen 1995, Cohen 2000) examines excess lung cancer mortality (over what is expected from county-wide smoking data) as a function of county mean indoor radon concentration, and finds a strong *negative* relationship. This relationship is quite robust, in the sense that it remains even if only a selected subset of counties is used: only urban counties, or only counties with above-average median family income, or only counties with near-median unemployment, or any of dozens of other categorizations. The nationwide relationship between county mean radon concentration and the county's excess lung cancer death rate is shown with a dashed line labeled "Cty-average" on Figure 2, which is based on a smooth curve through

Cohen's county-mean data for females, scaled so as to equal unity at a radon concentration of 0.

Taken at face value, Cohen's data suggest a rather strong protective effect from radon at residential concentrations. However, it is well known (e.g. Robinson 1950, Greenland et al. 1990, Greenland and Robins 1994, Gelman et al. 2001) that the "ecological fallacy" can lead to a spurious relationship in aggregated data. To give a classic example, Robinson (1950) found a positive correlation between statewide literacy (in English) and the fraction of residents who were foreign-born. This would suggest that the foreign-born were more likely to be literate, but in fact the reverse was true, and the observed effect in the aggregated data is due to the fact that more foreigners lived in states where the literacy of non-foreign-born people was high.

Cohen has argued (1995, 2000) that if lung cancer risk is linear in both smoking status and radon exposure, the deviation of the county mean curve from the standard model *cannot*, mathematically speaking, be due to correlations between radon and smoking unless there an almost perfect negative within-county correlation between these two variables. Lubin (2002) has shown that is not true, and suggests that a within-county correlation between smoking and radon is the likely cause of the discrepancy between the aggregate data and the standard model. He has demonstrated that if the degree of correlation between radon and smoking is itself related to the county mean radon concentration (in a very complicated and specific way, but not including extremely high negative correlation between radon and smoking status), then the county-aggregate results can be explained even if the individual-level risks are correctly predicted by the standard model.

Lubin's example demonstrates that confounding variables, even if not highly correlated with radon within counties, can cause effects of the correct magnitude to explain the county-aggregate data, even if the standard model is correct. However, the details of Lubin's example do not offer a plausible explanation, since his explanation requires very sharp shifts in the correlation between radon and lung cancer within counties, as a function of county mean radon concentration. Lubin's example works mathematically, but not realistically. Cohen's work does seem to invalidate the standard model at some level, but this does not mean that it tells us anything about radon risk, since the problem may lie (for example) with the standard model's assumed multiplicative interaction between smoking and radon, or with one or more additional within-county confounding variables.

Discussion of radon risk estimates

There is no question that exposure to very high concentrations of radon (and thus its decay products) causes cancer: the miner studies are quite convincing. Linear extrapolation to low doses and to residential breathing rates suggests that even radon concentrations that are commonly experienced may involve significant increased risk, but the expected risk is not high enough to easily test this hypothesis, given the large sources of uncertainty inherent in case-control and ecological studies.

Existing case-control studies, including over 5000 cases in all, are consistent with the standard model at 150 Bq/m^3, but even taken together are barely convincing (if that) in distinguishing the risk from zero, much less accurately quantifying it. Attempting to determine the exposure-risk curve at lower concentrations rapidly becomes even more problematic. Unless very significant resources are devoted to performing enormous case-control studies, epidemiological studies of radon risk will not yield a reliable exposure-risk curve for typical or even substantially elevated residential exposures, e.g. in the range from 100 to 400 Bq/m^3. There is little chance that a massive case-control study will be performed to address this problem.

As for ecological studies such as Cohen's (2000): mindful of the recognized problems with ecological studies, we have previously stated (Price 1995, Gelman et al. 2001) that ecological studies such as Cohen's examination of county-aggregate radon and lung cancer data "cannot be more than suggestive." We still feel that is true but would now tack on an important addendum: extrapolations from much higher exposures, and case-control studies involving a few hundred to a few thousand cases, *also* can be no more than suggestive. The county-average data do indeed constitute a challenge to the standard model, since, as Lubin's (2002) example illustrates, there appears to be no reasonable way to reproduce Cohen's data using a dose-response model that is linear in both smoking and radon. However, Lubin's example also confirms that the county-mean exposure-response curve can be completely uninformative of the personal exposure-response curve. Given the fact that the case-control studies are incompatible with a strong protective effect near 100 Bq/m^3, the county mean data do not seem to be useful for determining the risk from radon exposure.

As we've said before (Price 1995), life is rarely simple and it seems implausible that the exposure-risk curve could be perfectly linear all the way to zero exposure for both smoking and radon. Figure 3 shows several alternative exposure-risk curves, all but one of which are more or less consistent with the available case-control data; certainly more could be constructed. We are by no means proposing any of these as alternatives to the standard model, but rather wish to illustrate the nearly complete lack of convincing evidence about the shape of the curve below 200 Bq/m^3.

<INSERT FIGURE 3 ABOUT HERE>

The distribution of personal exposures within each county is very wide. In consequence, if the exposure-response curve is highly nonlinear, the county mean curve will not track the individual exposure-response curve, even in the absence of confounding variables or within-county correlation between radon and other variables. For example, consider the lowermost fictional exposure-response curve on Figure 3, which has a strong protective effect at low exposures (and is therefore incompatible with the results of case-control studies). To examine what such an exposure-response curve would imply in terms of county mean effects, in the absence of confounding, we assumed that (1) each person's exposure is a mixture of indoor exposure from their current residence, exposure from past residences, and outdoor exposure; (2) each individual source of exposure is lognormally distributed; (3) there is mild correlation between current and past residential exposure,

because people often move within the same county or region and there is some spaital correlation in radon levels. We used reasonable choices for the distributional parameters (which we will not discuss because we are merely trying to illustrate a point); results for predicted county mean exposure and response are shown with open circles on Figure 3 for counties across a range of average concentrations. The county mean results differ substantially from the individual exposure-response curve, showing a much smaller protective effect and very different behavior as a function of radon concentration.

As was recognized by Bogen (1998) in a cost-benefit analysis that considered a biologically plausible model for radon that includes a protective effect of low exposures, a protective effect at low concentrations could leave unchanged, or even increase, the expected benefit from radon reduction above 150 Bq/m^3. For instance, if the lowermost (protective) curve really did represent reality, then reducing the exposure from a pre-mitigation value of 200 Bq/m^3 to a post-mitigation value of 70 Bq/m^3 would provide a greater benefit than under the standard model. (If that curve really represented reality it would also make sense for more than half the people in the country to try to increase their exposure to radioactive gas.)

Given the lack of useful data on the exposure-response relationship below 200 Bq/m^3, it seems reasonable that radon policy analyses should at least consider the possibility of a nonlinear relationship. Lin et al. (1999) noted this point in performing a decision analysis concerning radon monitoring and mitigation: they first performed an analysis that assumed that the standard model holds, then repeated the analysis under the assumption that there is a risk threshold so that exposure to concentrations below 150 Bq/m^3 holds no risk at all, quantifying the differences in benefits of a nationwide mitigation program in both scenarios. Such exercises can at least highlight what factors in the exposure-risk curve are important for making policy decisions.

Implications for other aerosol exposure problems

Case-control studies of any environmental hazard are subject to uncertainty in both exposure and outcome, with the latter uncertainty often being due to small-sample variation in the number of cases in each exposure category. In the presence of such uncertainty, there will always be some exposure below which a risk cannot be distinguished from zero even if it exists.

Many current problems in the broader field of aerosol exposure share common elements with the radon question as outlined above:

1. There is convincing evidence of adverse health effects at elevated exposures, but no certainty about how to extrapolate to lower exposures;
2. Case-control studies are difficult because estimating past exposures is error-prone;
3. Ecological studies are vulnerable to confounding by variables (smoking, in the case of radon) that have effects that may be much larger than the effect from the exposure at issue.

In spite of sharing these characteristics with the radon problem, some aerosol epidemiology studies differ from it in important ways. Specifically, the only (observed or expected) health effects from radon involve lung cancer, which has a long latency period. There is no possibility of detecting immediate health consequences from a short-term increase in radon exposure. In contrast, exposure to some aerosols can cause immediate observed consequences, a fact that allows time-series analysis to be brought to bear, as in studies of the relationship between fine particle concentrations and cardiopulmonary mortality (Schwartz et al. 1994, Tsai et al. 2000, Maynard and Maynard 2002 and a great many others). We now briefly discuss epidemiological studies of the effects of fine aerosols.

Epidemiological studies of the effects of fine particle inhalation

Time-series studies of the health effects of fine particles

Time-series studies have the advantage of eliminating or greatly reducing many confounding effects found in other epidemiological studies. They can still be subject to confounding---for example, if more people die on days when airborne particle concentrations are high, that could be because high particle concentrations are associated with temperature, and high temperature is a risk factor for the frail. However, it is relatively easy to collect mortality and pollution data for many weeks, months, or even years, in which case confounding effects can be removed by stratifying on temperature, day of week, season, and so on.

Many studies have measured particle and gaseous pollutants and looked for a relationship with health outcomes such as death or hospital admissions. These studies usually measure particulate concentration parameters such as PM10 and PM2.5, usually along with some gaseous pollutants (such as ozone) and sometimes with some ability to resolve different types of particles, at one or more *outdoor* measurement locations. Summary statistics of these concentrations are then compared with health outcomes such as deaths due to heart or lung disease, hospital admissions, or other observables.

Particle measurements that are intended to characterize exposure are often subject to the major problem that the measurement location is spatially separated from the location(s) at which people are exposed. For example, pollutant measurements are often made outdoors at a few places in a city, whereas most people spend most of their time indoors (about 90%, in the United States). Thus, both the concentrations and size distributions of airborne particles to which people are exposed may be very different from the measurements. Given the reliance on remote ("ambient") outdoor concentration measurements, the relationship between such measurements and actual personal exposures is important. Table 1 summarizes results from several studies that investigated the relationship between ambient measurements (performed at one or more fixed monitoring locations in a city) and personal exposure measurements. In these studies, 24- or 48-hour personal exposure measurements were compared to 24- or 48-hour ambient monitoring data, and the correlation between the two types of measurement was determined. Some of the studies focused on populations believed to be at extreme risk, such as patients with chronic obstructive pulmonary disease or other cardiovascular disease; many of these are retirees and therefore not subject to workday exposures, so it

seems plausible that they would experience a different relationship between ambient and personal exposures. Other studies examined the relationship for healthy elderly or healthy adults. All studies found very substantial inter-subject variability in the correlation between ambient and personal exposure.

< INSERT TABLE 1 ABOUT HERE >

Several of the studies summarized in Table 1 have made the general claim that the correlation between ambient and personal exposures is high enough that ambient exposures can be used as a surrogate for personal exposure in epidemiological studies. That is false. If it were possible to control for, or eliminate, *all* confounding variables, then *any* correlation whatsoever between ambient and personal exposure could be used for epidemiology. But in practice it is impossible to completely eliminate or control all confounding variables, and a low correlation greatly diminishes the ability to separate the signal due to particle inhalation from the effects of confounders. Although a few of the studies found substantial correlations between ambient and personal exposures to PM2.5, several did not. The low correlations found in Basel and Nashville would prevent success of time-series studies there, if these values are correct for the at-risk populations in those cities. The higher, but still low, correlations in Boston and wintertime Baltimore would greatly reduce the statistical power of studies in those cities, again assuming those results hold for populations at risk from acute exposure to elevated air pollution.

The dismal ambient-personal correlations for some cities suggest that time series analyses will not work everywhere. However, in cities in which the correlation is substantial an effect of air-pollution-related mortality could be seen if it is big enough. An enormous number of such studies have been performed (a few recent ones are Moolgavkar et al. 1995, Samet et al. 2000 (with important corrections in Dominici et al. 2002a), Lee et al. 2000, Dominici et al. 2002b, Le Tertre et al. 2002) and the evidence for increased risk of daily mortality associated with increased particulate air pollution is irrefutable. Elevated mortality is definitely associated with increased PM2.5 levels, but the biologically important particle types cannot be conclusively determined because of the correlation between pollutants.

The time series studies do not quantify personal exposure, and certainly not dose. At present this is not an important failing, because peak urban air particulate concentrations are high enough to demonstrate increased mortality, but regulations are likely to lead to reduced peak concentrations, and eventually the discernable health effects may be too small to separate from the noise. Almost certainly, researchers will then attempt to reduce uncertainties in exposure, and perhaps dose, in order to extrapolate to lower exposures, as was the case with radon.

The time-series studies, although conclusive, have some serious shortcomings. One problem is that they cannot be used to estimate chronic effects: the number of pollution-related deaths is caused by a combination of chronic (long-term) and acute (short-term) exposure, and time-series studies are sensitive only to the second of these. Since elevated peak concentrations of particulate air pollution are harmful, it seems likely that chronic

exposure to somewhat lower concentrations also has an effect, but time series studies cannot resolve this issue because they rely on relating the *change* in daily death rate with the *change* in daily exposure. If the change in daily exposure is greatly reduced, the statistical power of these studies will be too low to allow estimating its effect.

Cohort studies of the health effects of fine particle inhalation

A cohort study collects data on individuals, following them over a long time period, and looks for an association between health outcomes and exposure to putative risk factors. Like all epidemiological studies, cohort studies can be subject to confounding because exposure is not the only thing that differs between groups. Cohort studies have several advantages over case-control studies: they often include personal exposure measurements (not in the case of particle exposure, but in other areas of research), they can include information on timing of exposures and other risk factors, and, like case-control studies, they can include person-specific information on confounding factors. This latter characteristic makes cohort studies enormously better than ecological studies, because it is possible to directly adjust for the effects of confounding variables at the individual level, thus avoiding the kinds of issues with the "ecological fallacy" that are discussed above for the case of radon. Of course there can still be confounding by a factor on which person-specific data were not collected.

Quite a few cohort studies of the effects of fine particle inhalation have been reported (Dockery et al. 1993, Pope et al. 1995, Shannon et al. 2001, for example). Almost all of these compare cohorts across cities---that is, they identify subjects who live in different cities, and follow them through time. These studies attempt to control for known risk factors, about which data are collected (examples include smoking, diet, age, obesity, fitness, and so on). However, there is still a large potential for error due to unknown confounding variables: lots of things vary between cities and it is hard to control for them all, or even to know what to control for. The reason multiple cities must usually be included is that individual subject exposure estimates aren't available: exposures are estimated for all subjects within a city, based on citywide monitoring data. These studies thus have one of the same major drawbacks as ecological regression---an inability to estimate individual exposures to the pollutant of interest---but with the key difference that known confounders can be controlled at the personal rather than group level.

Choosing subjects from within a single city or locale would be very advantageous for avoiding or minimizing the effects of confounding variables but would require an ability to estimate exposure either for individuals or for highly- and less-exposed groups within the city.

Ecological epidemiological studies of the health effects of fine particle inhalation

Several studies, which we will not bother to cite, have attempted to estimate effects of fine particle inhalation through ecological studies, comparing respiratory or cardiac mortality for high- and low-concentration cities. As with the example of ecological studies of radon, such results have very little quantitative value. No further studies of this type should be considered.

Inhalation modeling and experiments

Motivation for experiments and modeling related to lung deposition of aerosols

Any attempt to relate exposure to health effects through epidemiology is bound to fail at sufficiently low exposures: eventually the health effects will fall below the level at which they can be separated from the effects of confounding variables and statistical noise, even though the health effects may still have great practical significance at those levels. Moreover, even for health effects that can be convincingly identified or quantified through epidemiology, such quantification will often fail to answer important questions. For instance, epidemiological studies suggest that diesel engine exhaust may be carcinogenic at somewhat elevated exposures (McClellan, 1995). But diesel exhaust is a complex mixture of particles of varying chemical composition and epidemiology cannot tell us which, or which combination, is responsible for causing cancer, an important question for regulators and for engineers attempting to design better engines or exhaust filtration systems.

Although epidemiological studies are unable to address many important questions concerning aerosol inhalation, there is an alternative: all or part of the causal chain in Figure 1 can be modeled or determined experimentally. The ideal experiment would expose a human subject with known nasal, tracheal, and lung morphology, and known breathing rate and breathing volume, to a known size distribution of aerosol particles, and would measure the deposition as a function of size and precise location in the respiratory tract. In practice, neither lung morphology nor deposition as a function of size and location can be precisely determined in a living subject.

Gaining a complete understanding of the relevant parameters and phenomena is a rather ambitious task because the required experiments are difficult and many important physiological processes are not completely understood. Fortunately “ambitious” is not synonymous with “impossible,” and thanks to decades of research, computational models of deposition can be used with confidence for certain tasks. For example, for controlled breathing rates and known subject parameters (such as tidal volume), total deposition for particles larger than 0.01 micrometers can be predicted rather accurately over a wide range of conditions, at least for typical healthy adult subjects. Figure 4 shows a typical example, from Hofmann and Koblinger (1992). This comparison of predictions from two models to experimental data (the mean deposition in three healthy adult subjects) shows excellent agreement for the total deposition, and rather good but imperfect agreement for bronchial deposition at small particle sizes; unfortunately, experimental values for bronchial deposition of particles below 0.05 micrometers were not collected.

Although there are some differences between current deposition models that may have practical significance, most models currently in use agree with experiment and with each other rather well (e.g. see Bergmann et al. 1997 and Segal et al. 2000) over the size range from 0.01—10 micrometers and for typical adult lung parameters, which makes sense because any model that does not agree with experiment would be abandoned. There are some differences between the ICRP-66 model (ICRP 1994) and others for particles near and below 0.01 micrometers; Bergman et al. (1997) suggest that the ICRP model

overestimates deposition for those sizes, compared to experimental data (Heyder et al. 1986)

<INSERT FIGURE 4 ABOUT HERE>

Assessing uncertainties

There are two main causes of error in modeling aerosol deposition (or modeling anything, for that matter). The first is model misspecification: the model itself may simply be incorrect, failing to correctly include the effects of all significant parameters. The second is parameter error: even if the model is correct, predictions will be wrong if the input parameters are wrong.

No computational model involving physiological phenomena is perfect. One can hope, however, that the magnitude of model misspecification error is small, at least for the range of parameter values over which the model is intended to apply. Barring that, one at least hopes that the approximate magnitude of the error is known.

Unfortunately the magnitude of model misspecification error is notoriously difficult to evaluate. There are three basic approaches. The first is to compare the output of the model to experimental data. The error will be a combination of parameter error (discussed below) and model misspecification error. In performing this kind of test, it is important to compare the model to data that were *not* used to create it, or to estimate its parameters, in the first place; determining parameter values from one set of data and comparing the predictions to another set of data is called "cross-validation," and should be a standard procedure.

The second approach is to compare the model's output to that of another, superior model. For example, results from an analytical or semi-analytical deposition model might be compared to those from a computational fluid dynamics (CFD) simulation. The CFD simulation will itself be imperfect, but the comparison between the two models will still be informative as to roughly the size of the error that can be expected. One might ask, why not simply discard the inferior model, if another is known to be superior. Reasons can include a regulatory requirement to use the inferior model, or computational impracticalities of always using the superior one.

Finally, if direct experimental comparison is not possible and a definitely superior model does not exist, the last resort is to compare the model's output to that of other plausible models that tackle the same problem in different ways. Different models are likely to share some of the same flaws so that errors estimated this way may be understated. Still, if a researcher has several models at her disposal and they give different answers to the same problem, that is at least an indicator of the researcher's uncertainty, if not a measure of the model's intrinsic error.

As for the errors caused by incorrect input parameter values, the magnitudes of these errors are easy to evaluate if the uncertainty in the input parameters themselves is known. The most straightforward method, if the model is not too computationally burdensome, is

to perform Monte Carlo simulation: run the model repeatedly, using input values drawn from distributions around their "best guess" values, and summarize the variation in the output. Latin Hypercube sampling of the parameters is another possibility that provides similar results at a lower computational burden. Sampling approaches such as these are routine in many areas of research, and are just beginning to see use in the field of aerosol inhalation (Molokanov and Badjin 2000, Hofmann et al. 2002, Harvey and Hamby 2001 and 2002), where they should become routine.

Although total deposition and even regional deposition (that is, deposition in the trachea, bronchi, and alveoli) can be predicted quite well for a healthy subject, other quantities of interest cannot be predicted nearly so accurately. We now discuss the elements of the causal chain and the extent to which they are or are not fully understood.

General approach to assessing the effects of interpersonal variability

For a laboratory subject, it is possible to directly measure some model input parameters (such as tidal volume, inspiratory capacity, and so on). Other parameters (such as details of lung structure) cannot be measured. Therefore some parameters are known rather accurately and some will be estimated with error. Even in the absence of model misspecification, the error in input parameters will generate error in the model's prediction.

The range of the likely magnitude of the error, which is to say the uncertainty in the prediction, can be estimated from the uncertainty in the input parameters if the uncertainty is known. This uncertainty estimate can be made through analytical or semi-analytical techniques for some analytical deposition models, or through a Monte Carlo or Latin Hypercube sampling procedure for more complicated models or when the uncertainty is itself a complicated function. In essence, we create "virtual" people who share the same values for measured parameters but have different values for the other parameters; our subject is one of these people, but we don't know which.

Now consider making predictions for a group of people who are not laboratory subjets. For each person, now *all* of the input parameters are uncertain, in contrast to the laboratory case in which some parameters are known. Thus, the same approaches can be taken as in the case of estimating the uncertainty for an individual; the only difference is in the number of parameters for which statistical sampling is required.

Even though the predicted deposition for an unknown individual will be subject to error due to uncertainty in the input parameters, it may be possible to predict the distribution of deposition values across a population. We might know that the tidal volumes in a given group of subjects is approximately normally (Gaussian) distributed with a particular mean and standard deviation, but not know which individual has which tidal volume. Thus, the importance of intrapersonal variability depends on whether we are trying to make predictions for a specific individual, in which case our inability to determine the individual's input parameters is a source of error, or trying to make predictions for a population, in which case the inability to determine each individual's input parameters is irrelevant as long as we know their distribution across the population.

Respiratory tract morphology and other factors such as medical condition

There are three main issues concerning the effect of respiratory tract (especially lung) morphology on deposition:

1. Can current models predict important details of deposition for a given parametric description of the respiratory tract;
2. Do we have an acceptable parametric description of the respiratory tract; and
3. Do we have a parametric description of the intersubject variability of respiratory tracts.

These questions are, of course, interrelated. If models failed to predict quantities such as total and regional deposition, we would not know whether the problem is with (1) or (2), and there would be no point in trying to address (3). In fact, though, as illustrated by Figure 4 and as documented in, for example Hofmann (1996) and Segal et al. (2000), the total and regional deposition, averaged over at least a few experimental subjects, can be predicted rather well over a wide range of particle sizes. This fact seems to jointly answer the first two questions in the affirmative for total and regional deposition, although local deposition (that is, deposition for a given bronchial generation number or a particular location in the lung) is another story, as discussed below.

Intersubject morphometric variability

As for intersubject variability, models of the human respiratory tract are based on analysis of a relatively small number of human lung casts such as those summarized by Phalen et al. (1974), Yeh and Schum (1980), and Nikiforov and Schlesinger (1985). Available data show that there is significant intersubject variability in airway lengths, branching angles, and other relevant parameters (e.g. see Yu and Diu 1982, and Nikiforov and Schlesinger 1985).

In order to evaluate the practical significance of morphometric variability, Hofmann et al. (2002) evaluated the variation in output from a model that predicts local, regional, and total deposition, for ten different realizations of a stochastic lung model (Koblinger and Hofmann, 1985), and for particles ranging from 0.01 to 10 micrometers. (In this context, we use “local” to mean the bronchial generation, not the actual spatial location in the lung). The result is not a direct estimate of the effects of morphometric variability in real lungs; instead, it is an estimate of the effects of morphometric variability in lungs created by the stochastic lung model, given the assumption that the deposition model is correct.

The model predicted rather small intersubject variability in *total* deposition at all sizes (of the order of 15%), and somewhat larger variability in regional deposition (around 5% for particles between 0.1 micrometer and 1 micrometer, increasing to about 30% outside that range). However, in spite of the generally low intersubject variability in results for total and regional deposition, the variability in predicted local deposition was quite high: Figures 5 and 6 show predicted deposition as a function of generation number, for 1 and 10 micrometer particles, respectively. As the figure shows, predictions varied by nearly a factor of ten for large (10 micrometer) particles and low generation numbers, and by more than a factor of two for small (1 micrometer) particles and high generation numbers.

< INSERT FIGURE 5 AND 6 ABOUT HERE >

As Hofmann et al. report, their estimates of intersubject variability in total deposition are well in line with experimental data of Heyder et al. (1982) and Stahlhofen et al. (1981), but the estimated variability in regional deposition is somewhat less than Stahlhofen et al., a fact with several possible explanations (Hofmann et al., 2002). Two likely candidates are (1) the stochastic lung model (Koblinger and Hofmann 1985) may not include the full variation in human lung structures, and (2) the experiments of Stahlhofen et al. (1981) may not accurately measure local deposition, which was not directly observed but was estimated from particle clearance rates.

Modest intersubject variability in total and regional deposition had long been recognized (e.g. Heyder et al. 1982). It appears that at least some models of the variability of lung morphology (Koblinger and Hofmann 1985) can predict this variability in deposition. It is much less clear that current morphological models allow correct prediction of the variability in *local* deposition (or, for that matter, predict its mean value). Satoh et al. (1996) have examined a normal human lung and suggest there may be more *intra*-subject variability in the number of bronchial generations than is present in current morphometric models. Further work on this subject is required if either the inter- or intra-subject variability in *local* deposition are to be accurately assessed.

Site-specific deposition (deposition to a particular group of cells) is yet another issue. Currently, no single model predicts total, regional, local, and site-specific deposition; site-specific models consider only a very small portion of the lung, and often use CFD techniques rather than the semi-empirical or scaling-law-based techniques used by whole-lung models. Gradon and Pogorski (1996) and Hofmann (1996) discuss the extent to which current computational models can predict site-specific deposition, which is estimated to be highly variable even within a short section of airway, with at least an order of magnitude variation in deposition probability.

Site-specific deposition could ultimately prove important for dosimetry: if cellular response is nonlinear with respect to the number of particles absorbed by the cell (or in contact with it), the non-uniformity of deposition even in a given lung generation will influence the physiological response.

Systematic morphometric variability

There is evidence of moderate sex differences (on the order of 10 to 30%) in total deposition of aerosols in range of 3 to 5 micrometers, even for the same flow rates and lung volumes (Kim and Hu 1998). (In that study, “local” means a particular area of the lung, not a particular generation number).

Bennet et al. (1996) found that mean *fractional* deposition of 2 micrometer particles was independent of sex for resting adults over the range from 18 to 80 years, but that because males had 45% higher minute ventilation, so the deposition rate (deposition per unit time) was 30% greater in males than in females; this implies about the same deposition per unit

surface area of the lung (on average) in men and women. Bennet and Zeman (1998) extended these experiments to children as young as age 4: the fractional deposition of 2 micrometer particles was the same for children, adolescents, and adults, but the rate of deposition normalized to lung surface area was substantially higher for children. The results suggest that for resting breathing rates, gender- and even age-related differences in deposition of 2 micrometer particles are primarily due to breathing rates rather than morphological differences, although this may not be true at higher (non-resting) breathing rates. Chua et al. (1994) found no effect of age on local deposition in children with mild cases of cystic fibrosis, for children over six years old. Also, Nerbrink et al. (2002) report that using a standard lung deposition model predicted total deposition in asthmatic children with reasonable accuracy, for 1- to 2-micrometer particles.

Smith et al. (2001) report that the growth model for human lungs proposed by Phalen et al. (1985) accurately predicted airway parameters for subjects aged 3, 16, and 23 years (measured after autopsy). It seems that the characteristics of children's lungs that are important for total and regional deposition can be adequately predicted from the model of Phalen et al. or from scaling adult lung properties using the method of Habib et al (1994). This would probably not be true of infants, since the structure of the lung, and not just its scaling, changes substantially over the first two years of life.

Overall, it seems that current models should be sufficient for predicting deposition in healthy or nearly healthy children, but there is even less information about intersubject variability for children than for adults, so the distribution of deposition values over a group of children probably will not be predicted very well.

For the severely medically challenged, predictions will also be difficult. Brown et al. (2001) compared healthy adult subjects to adults with mild to moderate cystic fibrosis, and found substantial differences in regional deposition of 5-micrometer particles. Smaldone (2001) points out that patients with chronic obstructive pulmonary disease (COPD) have flow-limiting segments in the lung that will produce large local pressure drops and induce particle deposition in airways that do not experience deposition in healthy people. Kohlhaufl et al. (1999) found a modest (15%) increase in total deposition of 0.9 micrometer particles in women with airway hyperresponsiveness, compared to healthy women.

On the whole there seems to be a tendency for lung disease to lead to increased deposition. As Smaldone (2001) noted, diseased lungs can be morphologically different from healthy lungs (in addition to other, non-morphological differences), and it seems likely that accurate modeling of deposition in subjects with lung disease will require modifications to the morphometric models, for example to allow for more within-subject variability in bronchial diameters in a given generation, due to partially blocked airways.

Breathing rate and inhalation details

The quantity of aerosol inhaled and deposited is of course strongly dependent on breathing rate (volume inhaled per unit time). Laboratory inhalation experiments often involve controlled breathing, and essentially always involve measurements of the

breathing rate and tidal volume, so in such experiments there is seldom uncertainty in these important parameters.

Other inhalation details can also be important. For example, the short breath-hold time between inhalation and exhalation in normal breathing provides time for fine particles to settle gravitationally by a distance on the order of the size of an alveolar sac, so the length of breath-hold time (or its absence) can be an important parameter in some cases.

James et al. (1994) summarize and tabulate breathing data that were used in creating the ICRP-66 model and parameter input values (ICRP 1994). Inhalation rates vary greatly with age and activity: volume per unit time varies by a factor of 20 from infants to adults, and by a factor of 5 to 10 from resting to heavy exercise. In addition, for a given age and activity there is still substantial variation in both inhalation rate and in other inhalation-related parameters, such as fraction of air taken in through the mouth as opposed to the nose.

On the whole it appears that current parameterizations of inhalation are adequate for modeling, and that the main uncertainties with respect to the details of air intake are associated with interpersonal variability and activity-dependent breathing.

Clearance of the lung

Once deposited, particles are removed from the respiratory tract by several mechanisms, including coughing and phagocytosis. The most important mechanism is mucociliary transport: a thin film of mucous is continuously created in the bronchioles and, propelled by ciliary action, carries deposited particles eventually to the throat, where they are swallowed or expectorated. Because the particles are carried by the mucous layer, clearance velocities are nearly independent of particle size and material, with some exceptions. However, clearance times vary substantially with particle size because the deposition location varies strongly with size, a fact that can be exploited for estimating clearance rates for different parts of the lung.

Most experiments do not directly measure clearance as a function of location (or generation number) in the lung, instead measuring parameters such as total clearance as a function of time, from which local or regional mucous velocities are derived via a model for velocity as a function of location. As a result, models can predict total clearance quite well even if the local mucous velocities are completely wrong. Various quantitative clearance models have been proposed, but unlike deposition models the clearance models are not in very good agreement with one another as to clearance velocities, particularly for high generation numbers.

Figure 7 compares four models for clearance velocity as a function of generation number (Lee et al. 1979, Yu et al. 1986, and Cuddihy and Yeh 1988, Asgharian et al. 2001). In each case, a clearance time was assumed and the model was solved to determine velocity in each airway generation. The stochastic lung model (Koblinger and Hofmann 1985) used by Asgharian et al. (2001) differs from the other in having a lung morphology that is

assumed to be more realistic, having pathways that differ in the number of generations. < INSERT FIGURE 7 ABOUT HERE >

The tour du force analysis by Asgharian et al., which produced their results shown in Figure 7, used ten stochastic lung models, which produced slightly different velocity predictions (which would correspond to an effect of interpersonal differences in lung morphology); the standard deviation of the velocity predictions for the ten stochastic lungs is plotted in the figure. The effect on velocities is rather small. However, because different lungs have different distributions of total airway lengths, and because lung morphology affects both deposition and clearance, the results on clearance time can be rather profound. Asgharian et al. simulated the deposition and clearance of a distribution particles a mass-mean aerodynamic diameter of 1 micrometer, in their ten stochastic lungs, as well as in a standard symmetric lung model and in a typical lung path. Results are shown in figure 8. The differences in mass clearance profiles of the stochastic lungs suggest that even if there are no interpersonal differences in clearance physiology other than those caused by lung morphology, very large differences in mass removal rates are possible. This may reduce the need for individual-specific adjustable parameters such as the K factor in Yeates et al. (1982).

In addition to the obviously very large uncertainty in both typical clearance velocities and the amount of interpersonal variation in clearance velocities and times, other clearance-related parameters are very uncertain, and some important phenomena are not understood. A significant example is the presumed existence of a “slow clearance” mechanism to explain observed long-term (> 24 h) tracheobronchial retention of 1—3 micrometer particles, which seemed inconsistent with simple clearance models as discussed above. Explaining very slow clearance (>48 h) does require either the introduction of a mechanism other than mucosal transport (e.g. macrophage uptake), but, as the results of Asgharian et al. show, some long-term retention may be explicable purely on morphological grounds, even without a separate long-term clearance mechanism.

Another important phenomenon that is poorly understood is “overloading,” or dose-dependent decline of clearance. Overloading definitely occurs in rodents, but it is unclear whether it occurs in humans. Kuempel et al. (2000a and 2000b) examined this question by fitting a long-term clearance model to data on dust retention in miners, using dust loading data at autopsy and using estimated dust inhalation from work histories. Model fit was no better if an overloading mechanism was included.

Overall, quantitative modeling of clearance from the lung is very unreliable, and a great deal of progress is needed in order to improve predictions of clearance to the point where they can be used with confidence, as total and regional deposition models can, to make predictions for cases in which no experimental data are available. The degree of interpersonal variabiliy in the action of clearance mechanisms is even less certain.

As discussed by Bailey and Roy (1994) in an article in an annex to ICRP-66 that summarizes a prodigious volume of experimental literature, the ICRP-66 clearance model assumes the existence of a slow clearance mechanism, and provides

Estimating the dose-versus-exposure relationship in a population

Molokanov and Badjin (2000) performed Monte Carlo simulation to evaluate parameter sensitivity of the ICRP-66 model for internal dose due to plutonium inhalation. Harvey and Hamby (2001, 2002) examined the same model in considerably more detail. They compiled data from a variety of sources to estimate the mean and standard deviation in the general population for all person-specific model parameters, as a function of age. Their recommended distributions are shown in Table 2. They used Latin Hypercube sampling to generate parameters for individuals, for whom the regional deposition of a specified (1 micrometer AMAD) particle distribution was calculated from the ICRP-66 model. By repeating the sampling-and-calculation procedure many times, they created predicted distributions of regional deposition across the entire population of a given age and "breathing type" (mouth-breather or nose-breather). Results are shown in Figure 9 for two regions of the respiratory tract. Within each age group, distributions are very wide; most of the variability within each age group is due to the assumed interpersonal variation in breathing rate. Since the ICRP-66 model does not incorporate some known phenomena such as interpersonal morphological variation in the lung, the variability in results may be underestimated. Additionally, the sampling procedure assumes independence between the input parameters, whereas in fact they will be correlated (e.g. functional residual capacity will be positively correlated with diameter of trachea, since they both are correlated with body size); including such correlation could decrease or increase the widths of the predicted distributions, depending on details.

< INSERT FIGURE 9 ABOUT HERE >

Figure 9 clearly illustrates the problem of using exposure as a proxy for dose. For instance, about 5% of male nose-breathers are predicted to have an alveolar-interstitial deposition fraction less than 0.05, whereas about 5% of mouth-breathers are predicted to exceed 0.2, a factor of four difference which, as discussed above, is likely to be an underestimate. Of course, the distribution of physiological effects would be wider still, due to interpersonal variation in clearance, site-specific dose-response, and so on.

Of course, results such as these are only valuable to the extent that the model and assumptions on which they are based are trustworthy. The ICRP-66 model predicts regional deposition fairly well for a given set of parameter values, so the major issues in this particular case concern the accuracy of the statistical distributions of the input values.

Conclusion

Epidemiological studies definitively demonstrate increased mortality risk from exposure to very high concentrations of radon (several times higher than commonly occur in homes) and from surprisingly low concentrations of fine particles that are frequently experienced in cities. However, epidemiological studies based on exposure can only go so far in addressing questions related to the health effects of inhaled aerosols, because

they are subject to substantial uncertainties due to errors in exposure, response recording, and to the presence of confounding variables.

A quantitative understanding of the relationship between exposure and dose is required in order to interpret epidemiological studies and to extrapolate to conditions or populations outside the studies, and for many other purposes such as optimizing aerosolized drug delivery, predicting the effects of drugs that affect airway constriction or other physiological parameters, and so forth.

Total and regional deposition in typical human subjects can be predicted very well for a laboratory subject, as indeed has been the case for many years. Local deposition (deposition at a particular location in the lung, or for a particular branching generation) is subject to larger predictive error; it is unclear whether this is due to shortcomings in the models or to shortcomings of parametric characterizations of the lung, particularly for high branching generation numbers.

Interpersonal variability in morphology and inhalation parameters seems to be reasonably well characterized for healthy non-infants, but more work is needed on characterizing these factors for infants and for people with lung disease. Since the latter group is a population of particular concern with regard to fine particle air pollution, this issue merits more attention.

Ability to predict clearance is still not very good, and predictions certainly cannot be trusted for high generation numbers. Even some basic clearance-related questions are unanswered, such as what level of particle loading (if any) induces an "overload" response. A much better understanding of the distribution of clearance-related parameters is needed for the general population and particularly for patients with lung disease.

Table 3 shows a qualitative evaluation of the adequacy of models, parameter estimates, and estimates of interpersonal variability in parameters, with regard to predicting time-dependent dose from inhalation of particles in the range of 0.01—10 micrometers. Of course the adequacy of a model ultimately depends on what level of accuracy is required; the table should therefore be interpreted as characterizing the relative rather than absolute adequacy of the models and parameter estimates. At least in the size range from 0.01 to 10 micrometers, the challenges of predicting total and regional deposition have been met, and prediction of local dose is not bad. Clearance, interpersonal variability, and site-specific deposition constitute the new frontier, in the sense that uncertainties remain very high for predictions of those quantities.

< INSERT TABLE 3 ABOUT HERE >

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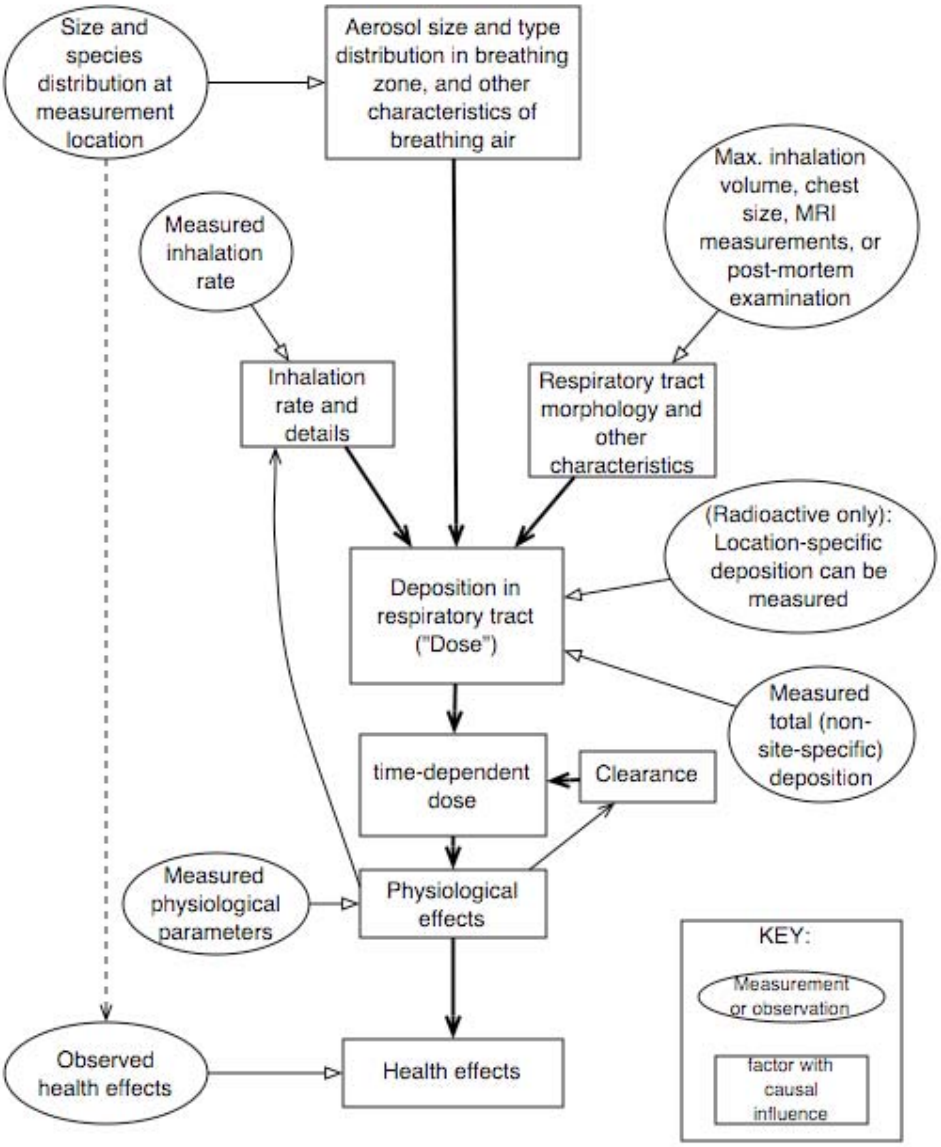

Figure 1: Schematic diagram showing the “causal chain” between aerosol inhalation and health effects (boxes), and the relationship of measurable parameters to physical or physiological quantities (ovals).

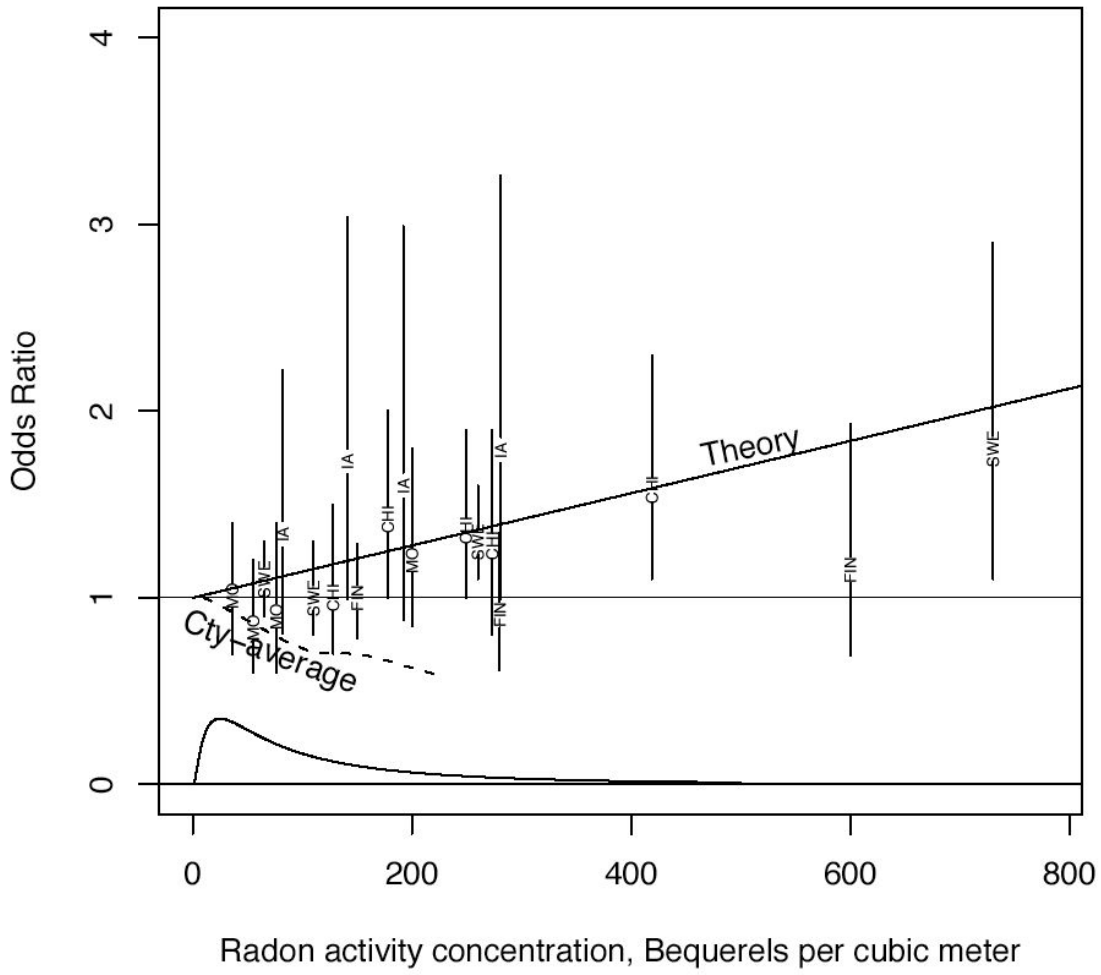

Figure 2: Estimated odds ratio (with 95% confidence bands) versus mean radon activity concentration, showing data from several case-control studies. The odds ratio estimates are labeled according to the state or country in which the study was performed: IA=Iowa (Field et al., 2000), CHI=China (Wang et al., 2002), FIN=Finland (Auvinen et al., 1996), SWE=Sweden (Pershagen et al., 1994), and MO=Missouri (Alavanja et al., 1994). The "Theory" line is an approximation to the prediction based on the standard model for risk due to radon and smoking (NRC 1998b). The "Cty-average" curve is a smooth fit to Cohen's (2000) data on smoking-adjusted excess of county lung cancer deaths and county-mean radon concentrations.

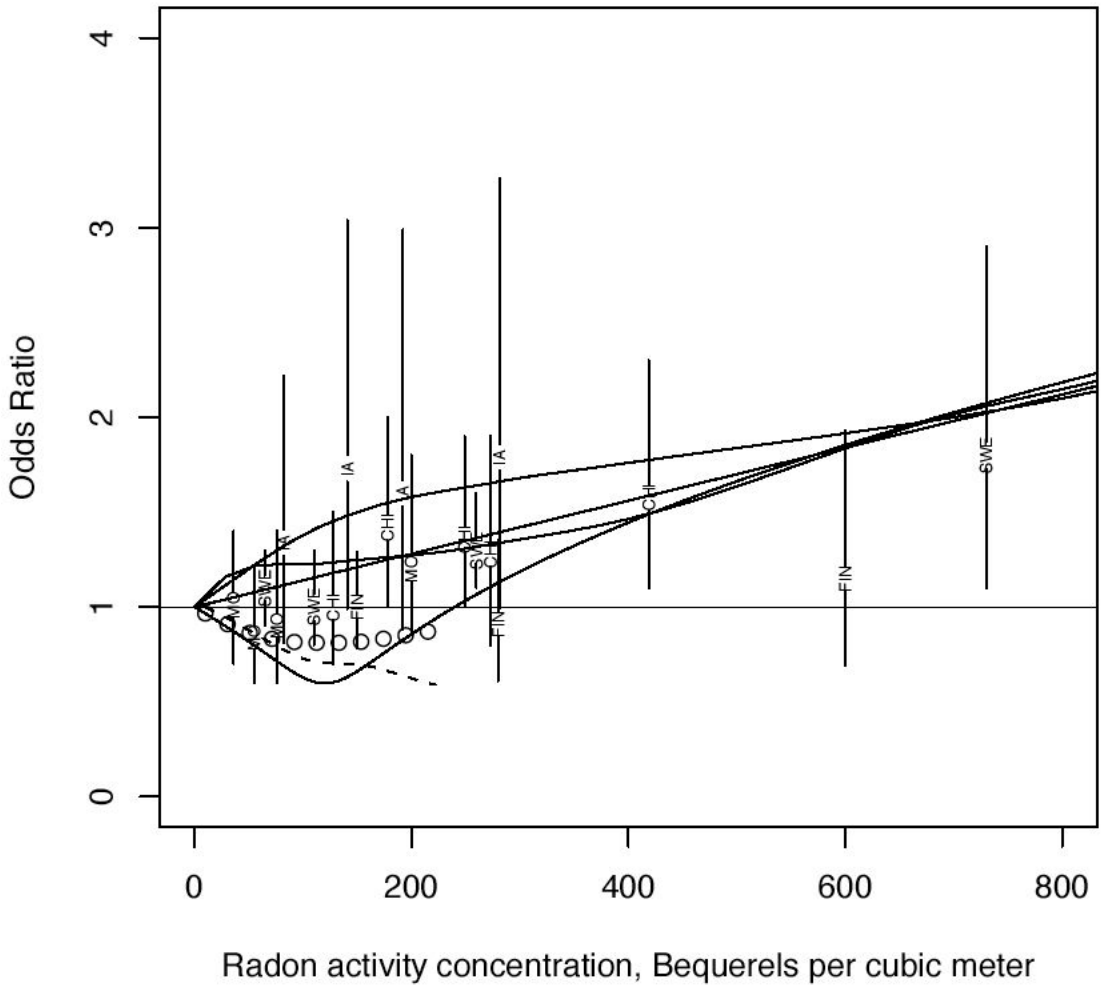

Figure 3: estimated odds ratio (with 95% confidence bands) versus mean radon activity concentration, showing data from several case-control studies. "Theory" line is an approximation to the prediction based on the standard model for risk due to radon and smoking (NRC 1998b). The "Cty-average" curve is a smooth fit to Cohen's (2000) data on smoking-adjusted excess of county lung cancer deaths and county-mean radon concentrations. Curves show hypothetical nonlinear individual dose-response functions. Points show county mean values if individual dose-response follows the lowest curve.

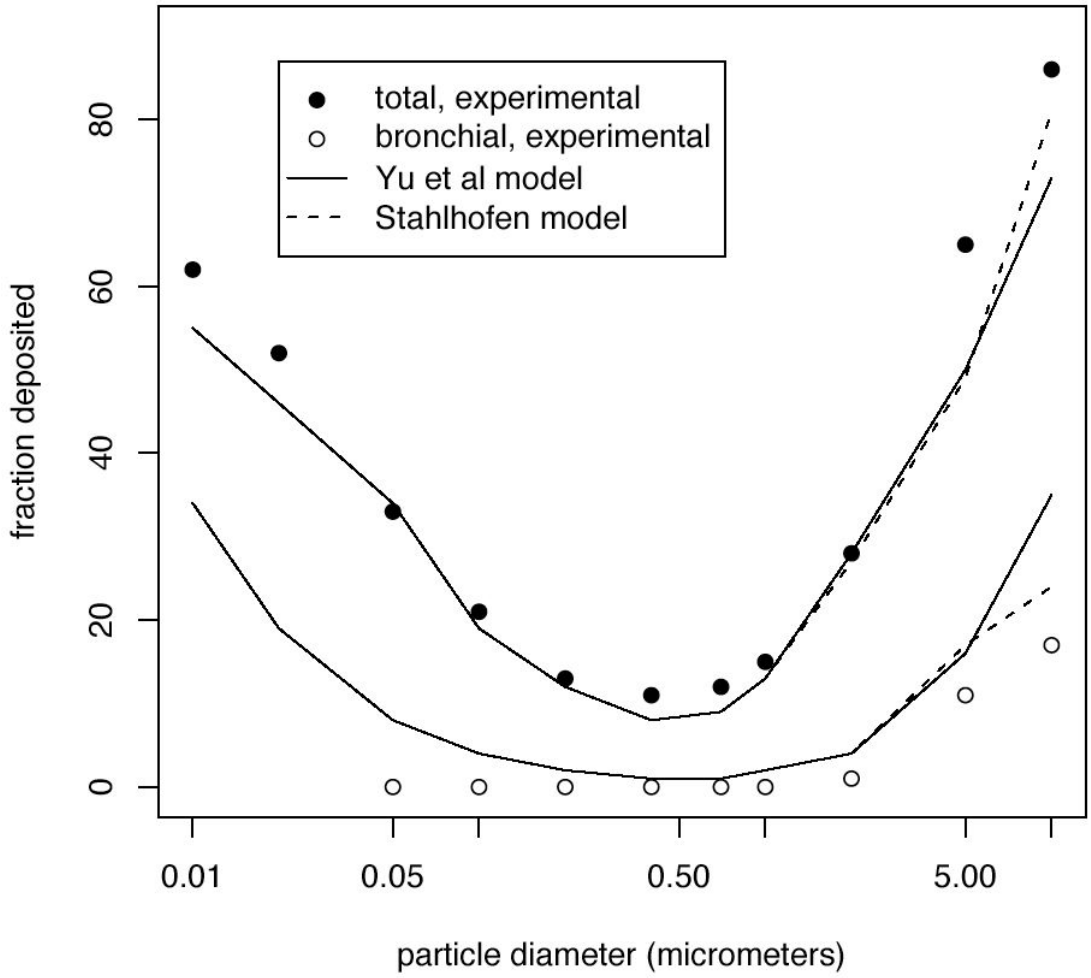

Figure 4: Points show total and bronchial deposition measured experimentally (citation needed *); lines are fits from two models. Both models overpredict bronchial deposition in the range 0.05—0.50 micrometers, but otherwise the fit is very good.

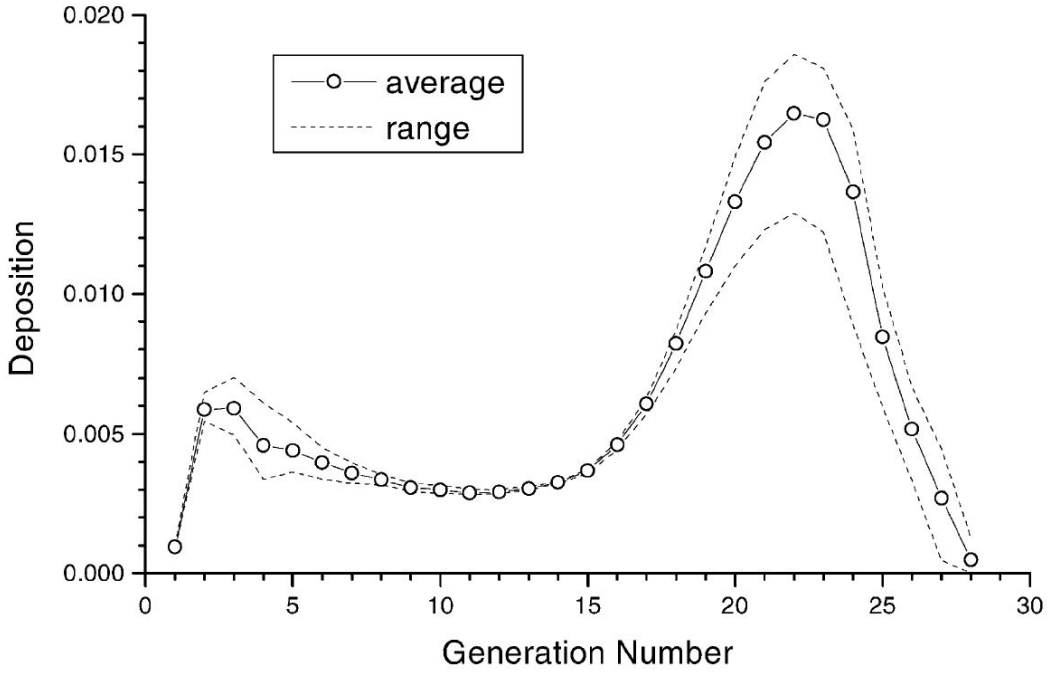

Figure 5: Predicted deposition versus generation number for 1 micrometer particles, showing the average and range of values predicted for ten stochastic lung models that attempt to capture interpersonal morphometric variability. Moderate interpersonal variability is predicted for generation number 18—28. Figure from Hofmann and Koblinger (1992).

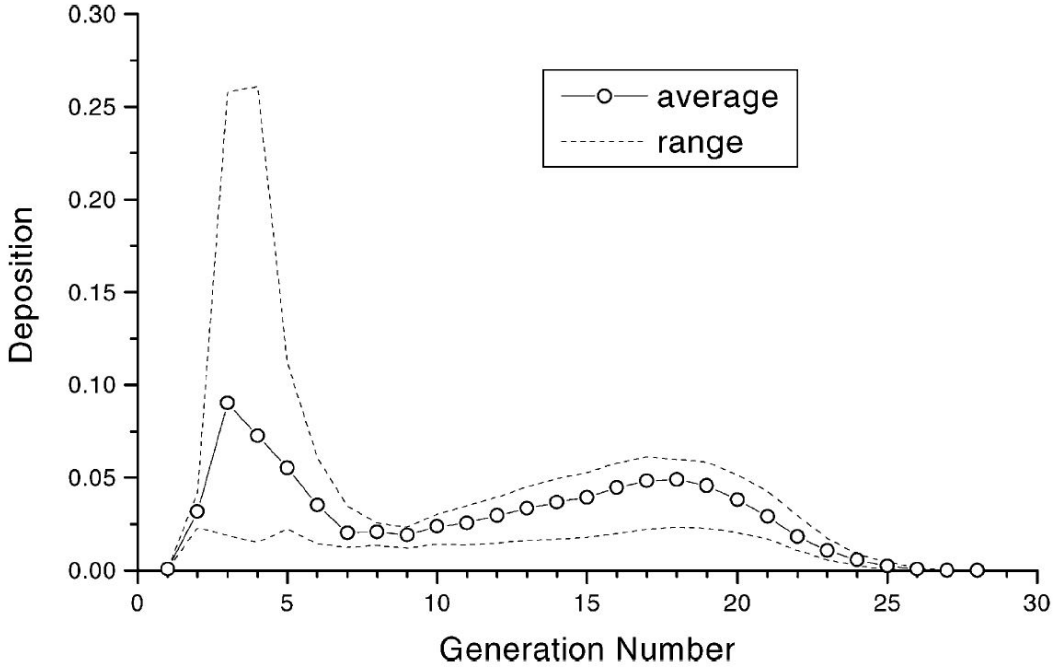

Figure 6: Deposition versus generation number for ten micrometer particles, showing the average and range of values predicted for ten stochastic lung models that attempt to capture interpersonal morphometric variability. The model suggests very high interpersonal variability in deposition as a function of generation number. Figure from Hofmann and Koblinger (1992).

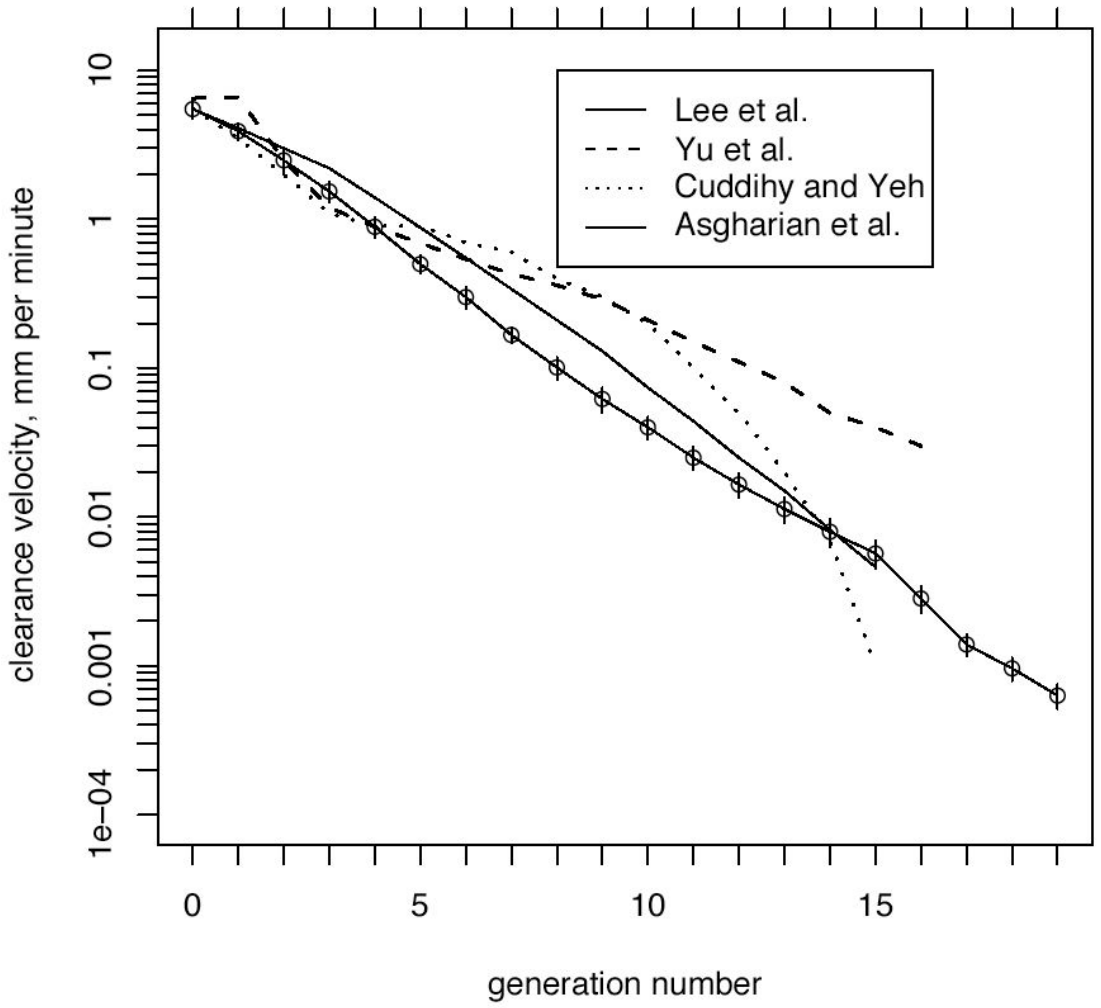

Figure 7: Predicted clearance velocity versus generation number for four deposition models, showing very large disagreement between models for generation numbers higher than five. The results for Asgharian et al. show the mean and standard deviation of predictions for ten stochastic lung models.

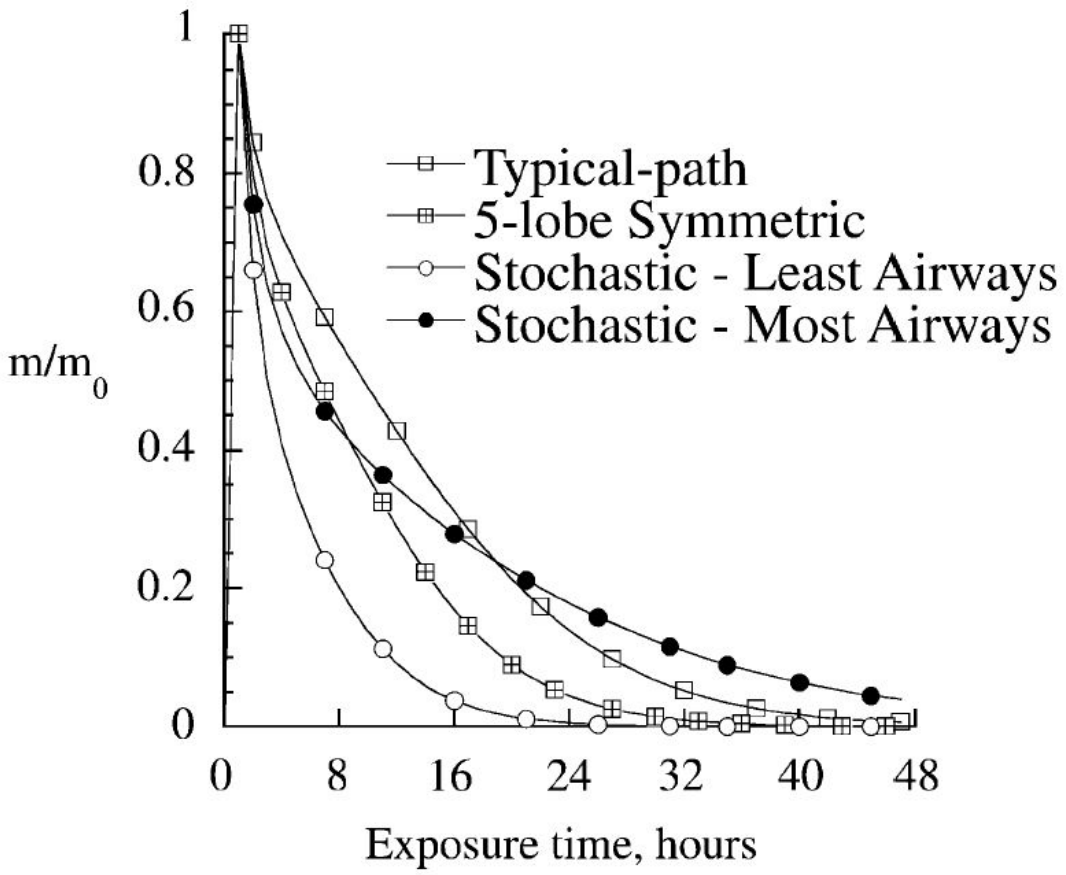

Figure 8: Predicted mass retained in the lung versus time, for four different model lungs. Results from two of ten stochastic lungs generated from the same parametric lung description are shown; the difference in mass clearance shows the predicted effect of interpersonal morphometric variability even for individuals with the same gross lung description. Predictions from a symmetric lung model and a typical particle path can be very different from an individual prediction using the stochastic model.

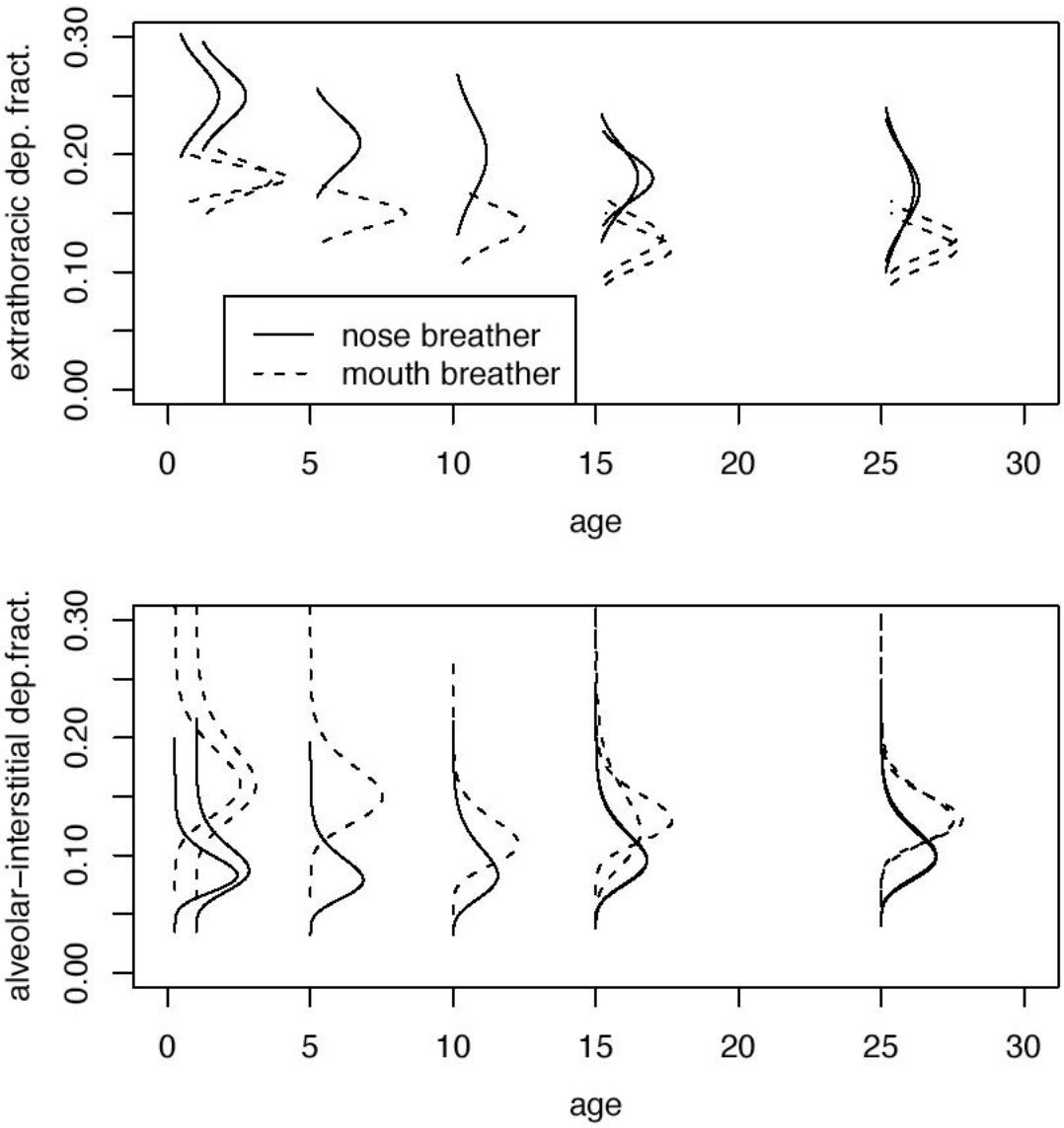

Figure 9: Predicted population distribution of extrathoracic and alveolar-interstitial deposition for 1 micrometer AMAD particles, as a function of age and breathing type, from Harvey and Hamby (2001) and (2002). Much of the width of the distribution for each group is attributable to the wide distribution of assumed breathing rates. Separate plots are shown for males and females at age 15 and 25 (adult), but are not labeled separately.

Table 1: Correlation between one- or two-day ambient outdoor measurements and personal exposure measurements for some populations; “patient” refers to treatment for chronic obstructive pulmonary disease.

Study population	Time period	Median r for PM2.5	Median r for SO4
Elderly patients in Vancouver (a)	Late spring through early fall	0.48	0.96
Elderly patients in Amsterdam (b)	Winter and spring	0.79	
Elderly patients in Helsinki (b)	Winter and spring	0.76	
Healthy elderly in Baltimore (c)	Summer	0.76	0.88
	Winter	0.25	0.72
Healthy adults in Helsinki (d)	Workdays (throughout year)	0.43	
	Leisure time (throughout year)	0.48	
Healthy adults in Basel (g)	Throughout year	0.07	
Patients in Nashville (e)	Summer	0.0	
Patients in Boston (f)	Winter and summer	0.3	

(a) Ebelt et al. (2000), (b) Janssen et al. (2000), (c) Sarnat et al. (2000) (d) Kousa et al. (2002), (e) Rojas-Bracho et al. (1996), (f) Rojas-Bracho et al. (1998), (g) Oglesby et al (2000).

Table 2: Suggested input parameter distributions simulate the general population, from Harvey and Hamby (2001) and (2002). Parameters show mean (standard deviation) of normal distributions. A proposed modification of the breathing rate parameterization is discussed in the text.

	Parameter (units)	adult male	adult female	15 y male	15 y female	10 y	5 y	1 y	3 mo
d_0	Diameter of trachea (cm)	1.65 (0.067)	1.53 (0.45)	1.59 (0.068)	1.52 (0.065)	1.31 (0.06)	1.06 (0.049)	0.75 (0.028)	0.62 (0.027)
d_9	Diameter of airway at gen. 9 (cm)	0.165 (0.067)	0.159 (0.006)	0.161 (0.007)	0.156 (0.007)	0.143 (0.007)	0.127 (0.006)	0.107 (0.004)	0.099 (0.004)
d_{16}	Diameter of airway at gen. 16 (cm)	0.051 (0.002)	0.048 (0.002)	0.047 (0.002)	0.045 (0.002)	0.039 (0.002)	0.031 (0.001)	0.022 (0.001)	0.020 (0.001)
BR	Breathing rate ($m^3\ h^{-1}$)	1.74 (0.67)	1.37 (0.45)	1.51 (0.51)	1.41 (0.45)	1.21 (0.41)	0.65 (0.19)	0.40 (0.11)	0.22 (0.06)
V_d	Anatomic dead space (mL)	146 (25.5)	124 (21.0)	130 (22)	114 (19)	78 (14.9)	46 (8.5)	20 (3.7)	14 (2.6)
FRC	Functional residual capacity (mL)	3301 (600)	2681 (500)	2677 (562)	2325 (488)	1484 (311)	767 (161)	244 (26)	148 (28)

Table 3: Qualitative view of the ability to predict the effects of morphology, inhalation details, and clearance on total and regional dose and time-dependent local dose for particles larger than 0.1 micrometer diameter, in an experimental subject (left columns) and across the general population (right columns). ++++ = very good, + = very poor.

	Ability to model the effects in a known individual			Ability to model the effects in the general population		
	Healthy adults	Children and elderly	Diseased	Healthy adults	Children and elderly	Diseased
morphology	++++	++++	+++	+++	+++	++
Inhalation details	++++	+++	+++	+++	+++	++
clearance	++	++	+	+	+	+
	Ability to predict particle deposition (dose)			Ability to predict population distribution of deposition, if exposure were known		
Total deposition	++++	+++	+++	+++	+++	++
Regional deposition	+++	++	++	++	++	+
	Ability to predict time-dependent dose, including clearance			Ability to predict population distribution of time-dependent dose		
Total	+++	+++	++	++	++	+
Regional	++	++	+	+	+	+
Local	+	+	+	+	+	+